

Application No. 10/076,071
Amendment dated September 7, 2005
Reply to Office Action mailed April 8, 2005

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-530 (Canceled).

531. (Currently amended) A method of treating an angiogenic disease or condition in an animal comprising administering to the animal an effective amount of a metal-binding peptide which does not have a metal ion bound to it the sequence of the peptide being:

$P_1 - P_2$,

wherein:

P_1 is:

Xaa₁ Xaa₂ His or

Xaa₁ Xaa₂ His Xaa₃,

the P_1 portion of the peptide being linear;

P_2 is (Xaa₄)_n;

Xaa₁ is the N-terminal amino acid of the peptide, the only substituents on the α -amino group of Xaa₁ are hydrogen ~~has an unsubstituted α -amino group~~, and Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

532. (Previously presented) The method of Claim 531 wherein:

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, glutamic acid, lysine, hydroxylysine, histidine, arginine, or α -hydroxymethylserine, and

Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, glutamine, cysteine, methionine, lysine, hydroxylysine, histidine, arginine, or α -hydroxymethylserine.

533. (Previously presented) The method of Claim 531 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, threonine or α -hydroxymethylserine.

534. (Previously presented) The method of Claim 531 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

535. (Previously presented) The method of Claim 531 wherein Xaa₃ is lysine.

536. (Previously presented) The method of Claim 531 wherein:

Xaa₁ is aspartic acid, glutamic acid, arginine, lysine, threonine, serine or α -hydroxymethylserine,

Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and

Xaa₃, when present, is lysine.

537. (Previously presented) The method of Claim 536 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine or α -hydroxymethylserine.

538. (Previously presented) The method of Claim 537 wherein Xaa₂ is glycine, alanine, valine, leucine or isoleucine.

539. (Previously presented) The method of Claim 538 wherein P₁ is Asp Ala His or Asp Ala His Lys.

540. (Previously presented) The method of Claim 539 wherein P₁ is Asp Ala His Lys.

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541. (Previously presented) The method of Claim 536 wherein Xaa₁ is arginine, lysine, threonine, serine or α -hydroxymethylserine, and Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine or α -hydroxymethylserine.

542. (Previously presented) The method of Claim 541 wherein P₁ is Thr Leu His, HMS HMS His or Arg Thr His.

543. (Previously presented) The method of Claim 531 wherein n is 0-10.

544. (Previously presented) The method of Claim 543 wherein n is 0-5.

545. (Previously presented) The method of Claim 544 wherein n is 0.

546. (Previously presented) The method of Claim 531 wherein P₂ comprises a metal-binding sequence.

547. (Previously presented) The method of Claim 546 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,
(Xaa₄)_m His Xaa₂ Xaa₅,
(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or
(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

548. (Previously presented) The method of Claim 547 wherein Xaa₅ is Orn or Lys.

549. (Previously presented) The method of Claim 546 wherein P₂ comprises one of the following sequences:

[(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,
[(Xaa₄)_mXaa₅Xaa₂His]_r,
[(Xaa₄)_mXaa₅Xaa₂HisXaa₃(Xaa₄)_mXaa₅Xaa₂His]_r, or
[(Xaa₄)_mXaa₅Xaa₂His(Xaa₄)_mXaa₅Xaa₂HisXaa₃]_r,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂, m is 0-5 and r is 2-100.

550. (Previously presented) The method of Claim 546 wherein P₂ comprises a sequence which binds Cu(I).

551. (Previously presented) The method of Claim 550 wherein P_2 comprises one of the following sequences:

Met Xaa₄ Met,
Met Xaa₄ Xaa₄ Met,
Cys Cys,
Cys Xaa₄ Cys,
Cys Xaa₄ Xaa₄ Cys,
Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,
Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],
Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],
Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or
 γ -Glu Cys Gly.

552. (Previously presented) The method of Claim 551 wherein P_2 is Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9].

553. (Previously presented) The method of Claim 531 wherein P_2 comprises a sequence which enhances the ability of the peptide to penetrate cell membranes, reach target tissues, or both.

554. (Previously presented) The method of Claim 553 wherein P_2 is hydrophobic or an arginine oligomer.

555. (Previously presented) The method of Claim 531 wherein at least one of the amino acids of P_1 other than β -alanine, when present, is a D-amino acid.

556. (Previously presented) The method of Claim 555 wherein Xaa₁ is a D-amino acid or His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

557. (Previously presented) The method of Claim 555 wherein all of the amino acids of P_1 other than β -alanine, when present, are D-amino acids.

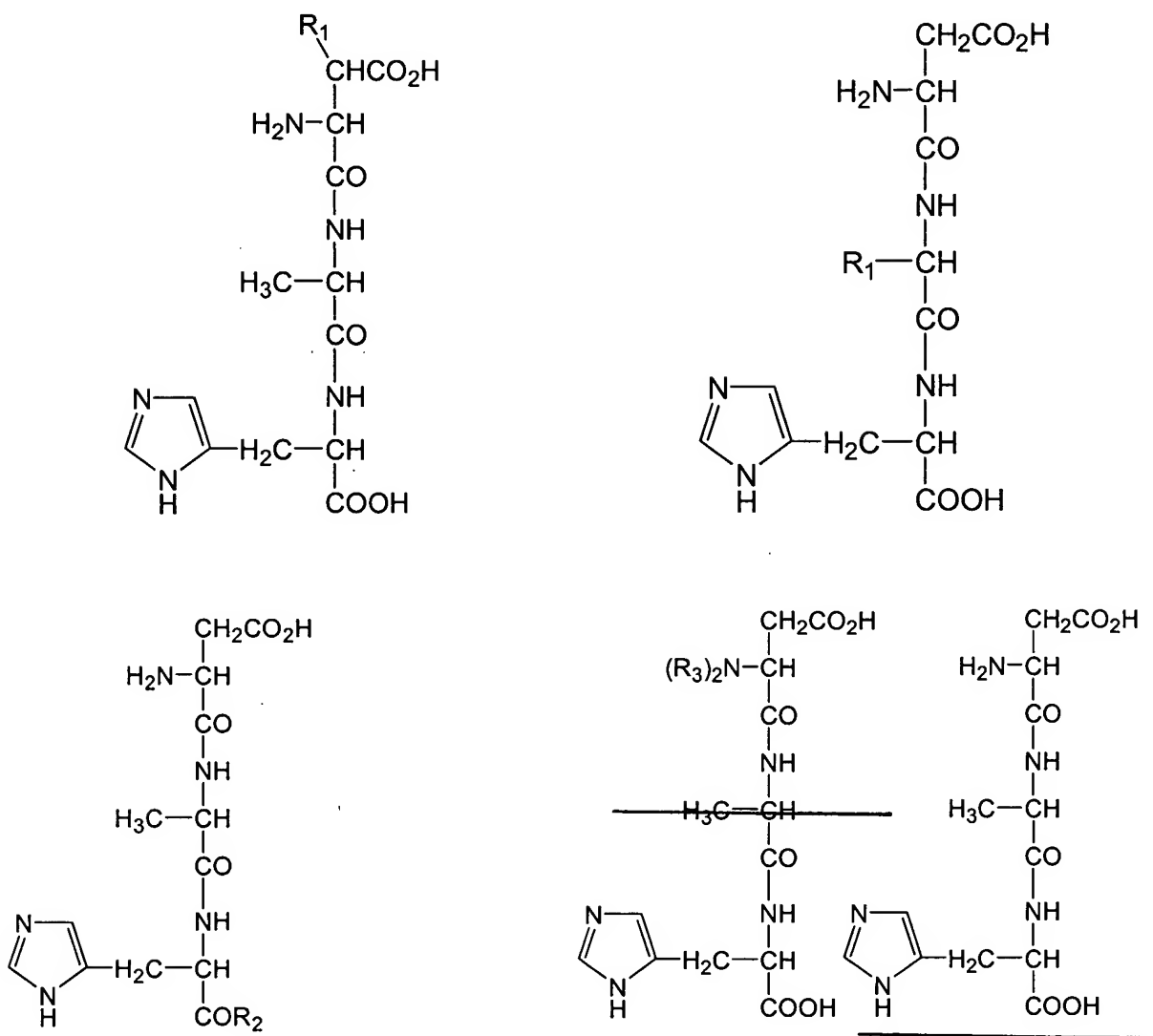
558. (Previously presented) The method of Claim 555 wherein at least 50% of the amino acids of P_2 are D-amino acids.

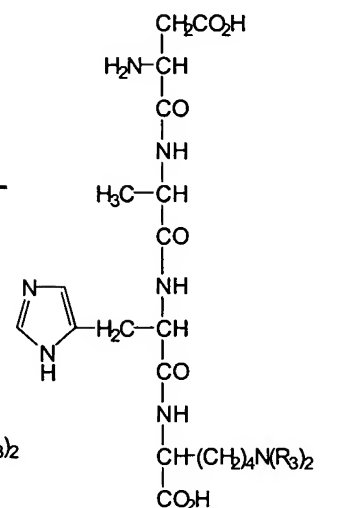
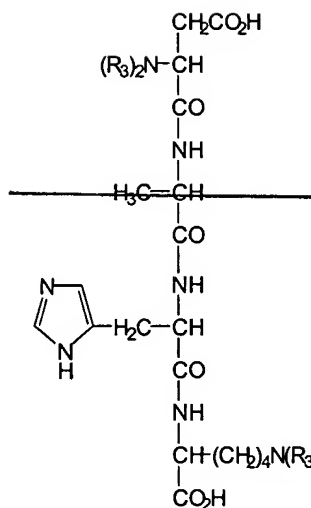
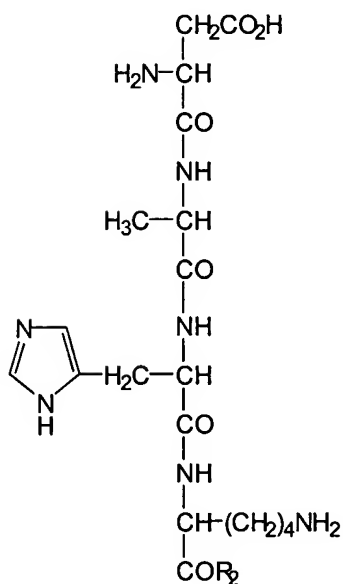
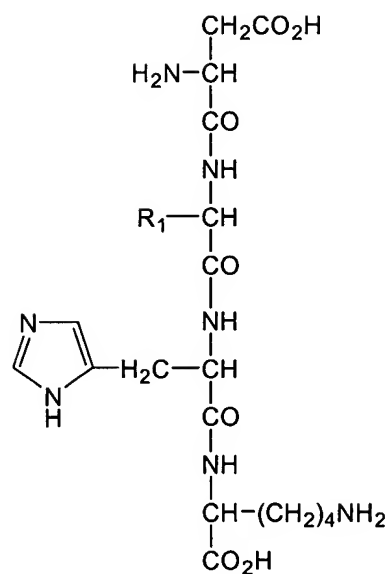
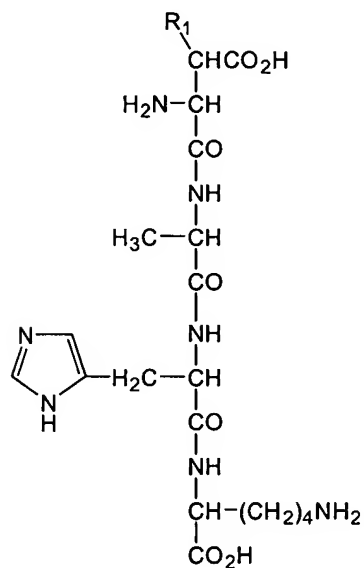
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559. (Previously presented) The method of Claim 531 wherein at least one amino acid of P_1 or at least one amino acid of P_2 , or at least one amino acid of P_1 and at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

560. (Previously presented) The method of Claim 559 wherein the terminal $-\text{COOH}$ of P_1 - P_2 is substituted to produce $-\text{COR}_2$, wherein R_2 is $-\text{NH}_2$, $-\text{NHR}_1$, $-\text{N}(\text{R}_1)_2$, $-\text{OR}_1$, or $-\text{R}_1$, wherein R_1 is an alkyl, aryl or heteroaryl.

561. (Currently amended) The method of Claim 559 wherein n is 0 and P₁ has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $-N(R_1)_2$, $-OR_1$, or $-R_1$; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together

form a non-peptide, metal-binding functional group.

562. (Previously presented) The method of Claim 561 wherein R_2 is $-NH_2$.

563. (Previously presented) The method of Claim 531 wherein the method further comprises administering an effective amount of another metal-binding compound in combination with the peptide.

564. (Previously presented) The method of Claim 563 wherein the metal-binding compound binds iron.

565. (Previously presented) The method of Claim 564 wherein the iron-binding compound is deferoxamine mesylate.

566. (Previously presented) The method of Claim 563 wherein the metal-binding compound binds Cu(I).

567. (Previously presented) The method of Claim 566 wherein the Cu(I)-binding compound is a peptide.

568. (Previously presented) The method of Claim 567 wherein the Cu(I)-binding peptide comprises one of the following sequences:

Met Xaa₄ Met,

Met Xaa₄ Xaa₄ Met,

Cys Cys

Cys Xaa₄ Cys,

Cys Xaa₄ Xaa₄ Cys,

Met Xaa₄ Cys Xaa₄ Xaa₄ Cys,

Gly Met Xaa₄ Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:7],

Gly Met Thr Cys Xaa₄ Xaa₄ Cys [SEQ ID NO:8],

Gly Met Thr Cys Ala Asn Cys [SEQ ID NO:9], or

γ -Glu Cys Gly,

wherein Xaa₄ is any amino acid.

569. (Previously presented) The method of any one of Claims 531-568 wherein the

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angiogenic disease or condition is a neoplastic disease, a connective tissue disorder, psoriasis, an ocular angiogenic disease, a cardiovascular disease, a cerebral vascular disease, hemophiliac joints, an immune disorder, a benign tumor, hypertrophy, endometriosis, polyposis, or obesity.

570. (Previously presented) The method of Claim 569 wherein the angiogenic disease or condition is a neoplastic disease.

571. (Previously presented) The method of Claim 570 wherein the neoplastic disease is a tumor.

572. (Previously presented) The method of Claim 571 wherein the tumor is located in the bladder, brain, breast, kidney, liver, pancreas, lung, cervix, ovary, prostate, stomach, intestines, colon, rectum, or uterus.

573. (Previously presented) The method of Claim 570 wherein the neoplastic disease is tumor metastasis.

574. (Previously presented) The method of Claim 569 wherein the angiogenic disease or condition is psoriasis.

575. (Previously presented) The method of Claim 569 wherein the angiogenic disease or condition is an ocular angiogenic disease.

576. (Previously presented) The method of Claim 575 wherein the ocular angiogenic disease is macular degeneration.